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UTDRAG UR DATABASEN PLUSPAT PER 2001-03-20

PLUSPAT - (C) QUESTEL-ORBIT
Patent Number :
JP11302156 A 19991102 [JP11302156]
Title of the Invention :
(A) ATOMIZATION OF POLYPEPTIDE
Patent Assignee :
(A) TANABE SEIYAKU CO
Inventor :
(A) SUZUKI TAKEHIKO; MORITA TAKAHIRO; YAMAHARA HIROSHI
Application Data :
JP10527298 19980416 [1998JP-0105272]
Priority Details :
JP10527298 19980416 [1998JP-0105272]
IPC (issuing Office) :
(A) A61K-009/14 A61K-047/30
Publication Stage :
(A) Doc. Laid open to publ. Inspec.
Abstract of the Invention :
PROBLEM TO BE SOLVED: To obtain fine particles of high purity polypeptide in high recovery rate without being accompanied by any degeneration by adding a specific organic solvent after lyophilizing a mixed aqueous solution of polypeptide and polyethylene glycol.

SOLUTION: The subject fine particles preferably having average particle size <+10 .mu.m is obtained by adding the organic solvent (C) in which the constituent (A) is insoluble but the constituent (B) is soluble, after lyophilizing the mixed aqueous solution of polypeptide (A) preferably having molecular weight of 1,000 to 200,000 more preferably, 5,000 to 70,000 and polyethylene glycol (B) of molecular weight; 400 to 500,000 more preferably 2,000 to 100,000. Hormones or enzymes or cytokines or growth promoting substances are cited as the constituents (A). Methylene chloride or acetone or ethyl acetate or ethanol or the like are cited as the constituents (C). The preferable concentration ratio of the constituents (B)/(A) is more than the phase inversion point, such as >=0.25.

UTDRAG UR DATABASEN WORLD PATENTS INDEX PER 2001-03-20

DWPI - (C) Derwent
Accession Nbr :
2000-065699 [06]
Sec. Acc. CPI :
C2000-018806
Title :
Atomisation of polypeptide used for treatment of various diseases - involves lyophilisation of mixed aqueous solution of polypeptide and polyethylene glycol
Derwent Classes :
A25 A96 B04 C03
Patent Assignee :
(TANA) TANABE SEIYAKU CO
Nbr of Patents :
1
Nbr of Countries :
1
Patent Number :
JP11302156 A 19991102 DW2000-06
A61K-009/14 11p *
AP: 1998JP-0105272 19980416
Priority Nbr :
1998JP-0105272 19980416
IPC s :
A61K-009/14 A61K-047/30
Basic Abstract :
JP11302156 A
NOVELTY - A mixed aqueous solution containing polypeptide and polyethylene glycol is lyophilised. An organic solvent which dissolves polyethylene glycol is added to the obtained solid substance.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for manufacture of microsphere particles which involves preparing an oil phase by adding in vivo degradable polymer and a volatile organic solvent of low solubility in water and solidifying the degradable polymer in the oil phase.

USE - For treatment of various diseases.

ADVANTAGE - Polypeptide microparticle of high purity is manufactured efficiently. Microparticle recovery is high and re- dispersibility is favourable. Release of polypeptide is carried out for long period of time at fixed velocity. Atomisation of polypeptide is carried out without requiring any modification. (Dwg.0/0)
Manual Codes :
CPI: A05-H03 A12-V01 B04-C01 C04-C01
B04-C03C C04-C03C B12-M11E C12-M11E
Update Basic :

2000-06

JAPANESE [JP,11-302156,A]

CLAIMS DETAILED DESCRIPTION TECHNICAL FIELD PRIOR ART EFFECT OF THE INVENTION TECHNICAL PROBLEM MEANS EXAMPLE DESCRIPTION OF DRAWINGS DRAWINGS

[Translation done.]

* NOTICES *

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CLAIMS

[Claim(s)]
[Claim 1] It is the atomization technique of the polypeptide characterized by a polyethylene glycol adding the organic solvent which may be melted although it freeze-dries and a polypeptide cannot melt a polypeptide and the mixed aqueous solution of a polyethylene glycol in the obtained solid.
[Claim 2] The atomization technique of a polypeptide according to claim 1 that the rate of the ratio of concentration of the polyethylene glycol/polypeptide of the mixed aqueous solution is more than phase inversion proportion.
[Claim 3] The atomization technique of a polypeptide according to claim 1 that the rate of the ratio of concentration of the polyethylene glycol/polypeptide of the mixed aqueous solution is 0.25 or more.
[Claim 4] The atomization technique of a polypeptide according to claim 1, 2, or 3 that the molecular weight of a polypeptide is 5000-70000.
[Claim 5] The atomization technique of a polypeptide according to claim 1, 2, 3, or 4 that the molecular weight of a polyethylene glycol is 400-500000.
[Claim 6] The atomization technique of a polypeptide according to claim 1, 2, 3, or 4 that the molecular weight of a polyethylene glycol is 2000-100000.
[Claim 7] The atomization technique of a polypeptide according to claim 1, 2, 3, or 4 that the molecular weight of a polyethylene glycol is 6000-70000.
[Claim 8] The atomization technique of a polypeptide according to claim 1 or 4 that the molecular weight of a polyethylene glycol is 6000-70000, and the rate of the ratio of concentration of the polyethylene glycol/polypeptide of the mixed aqueous solution is more than 102.7/M0.68 (molecular weight of M:polypeptide).
[Claim 9] It is the atomization technique of the polypeptide of a claim 1-8 given in any one term that the organic solvent which may melt a polyethylene glycol is one sort chosen from the group which it becomes from a methylene chloride, chloroform, an acetone, an acetonitrile, ethyl acetate, toluene, a methanol, and ethanol, or two sorts or more although a polypeptide must have been melted.
[Claim 10] Polypeptide particle suspension obtained by the technique of a claim 1-9 given in any one term.
[Claim 11] Polypeptide particle suspension according to claim 10 whose mean particle diameter of a polypeptide particle is 10 micrometers or less.
[Claim 12] Polypeptide particle powder which removes a polyethylene glycol and an organic solvent and is obtained from the polypeptide particle suspension obtained by the technique of a claim 1-9 given in any one term.
[Claim 13] The process of the microsphere tablet characterized by adding the organic solvent with low solubility and biodegradation nature polymer to water to the polypeptide particle powder which removes a polyethylene glycol and an organic solvent and is obtained from the polypeptide particle suspension obtained by the technique of a claim 1-9 given in any one term for the volatility which may melt a biodegradation nature polymer, preparing an oil phase to it, and making it solidify the biodegradation nature polymer in this oil phase.
[Claim 14] It is the process of the microsphere tablet characterized by for a polyethylene glycol and a biodegradation nature polymer adding the organic solvent with low solubility and biodegradation nature polymer to water for the volatility which may be melted although a polypeptide cannot melt a

polypeptide and the mixed aqueous solution of a polyethylene glycol in the solid obtained by freeze-drying, and preparing an oil phase, and solidifying the biodegradation nature polymer in this oil phase.

[Claim 15] The process of the microsphere tablet according to claim 13 or 14 which a biodegradation nature polymer is two or more sorts, and oil phases are O / O type emulsion, and are O/O / W type emulsion liquid drying characterized by for the solidification means of a biodegradation nature polymer distributing O / O type emulsion underwater, preparing O/O / W type emulsion, and subsequently drying this among liquid.

[Claim 16] The microsphere tablet obtained by technique according to claim 13, 14, or 15.

[Translation done.]

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TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] The purpose of this invention has high recovery and it is in offering the technique of preparing the polypeptide particle of a high grade, without being accompanied by denaturation.

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[The technical field to which invention belongs] this invention relates to the atomization technique of a polypeptide.
[0002]
[Description of the Prior Art] In recent years, the polypeptide which has a physiological activity is widely used for the treatment of the various morbus of the Homo sapiens or an animal, and the prevention.
[0003] Conventionally, although almost all cases were prescribed for the patient by injection every day, as for these polypeptides, the simpler medication method is examined from problems, such as the complicatedness of the prescribing [a medicine / for the patient] method, and a burden to a patient.
[0004] Transpulmonary administration is raised as an example of such technique. However, since parvus grain can reach in an alveoli pulmonis in transpulmonary administration, in order to make it reach in an alveoli pulmonis certainly, it is necessary to carry out the atomization of the polypeptide.
[0005] Moreover, by enclosing a polypeptide into a biodegradation nature polymer and considering as a microsphere, long-term gradual release-ization is attained and the study which carries out part medication of this by injection in the living body is also advanced.
[0006] The method of emulsifying the aqueous solution of a polypeptide first in organic solvents, such as a methylene chloride in which the biodegradation nature polymer was melted, preparing W / O emulsion, emulsifying this underwater, and obtaining a microsphere as a process of such a microsphere, is learned.
[0007] However, generally, when many of polypeptides contact an organic solvent in the status that it melted in water, it receives denaturation and has the problem will lose activity.
[0008] Although distributing a polypeptide in the organic solvent in which the biodegradation nature polymer was melted with powder, considering as an oil phase, and preparing a microsphere using this is also examined in order to avoid this problem In this technique, since the abundant exudation (initial-burst phenomenon) in the early stages of elution would arise when the high rate of inclusion is not obtained if the particle diameter of a polypeptide is large, the atomization of the polypeptide needed to be carried out like the aerosol tablet.
[0009] The mixed aqueous solution of the technique (JP,4-36233,A) and (2) water-soluble polypeptide which carry out the atomization of the mixed aqueous solution of water-soluble-polymer matter, such as (1) gelatin, and a water-soluble polypeptide, using a spray dryer as the atomization technique of a polypeptide, and the water-soluble-polymer matter is freeze-dried, the technique (JP,8-225454,A) and (3) surfactants which pulverize this freeze-drying object using a jet mill, and a polypeptide are mixed underwater, and the technique (JP,9-315997,A) of carrying out the quick drying of this etc. is raised.
[0010] However, for this reason, in order that both the technique of (1) and (2) preventing deactivation of a polypeptide from heat or a physical collision, a lot of water-soluble-polymer matter was blended, when not obtained, the recovery of the polypeptide particle of a high grade was also very low, in the technique of (3), since the surfactant was used, the spacial configuration changed and it had the problem of losing a physiological activity according to the modality of polypeptide.

[0011]
[Problem(s) to be Solved by the Invention] The purpose of this invention has high recovery and it is in offering the technique of preparing the polypeptide particle of a high grade, without being accompanied by denaturation.
[0012]
[Means for Solving the Problem] Although a phase separation happens among both and the polypeptide could not be melted in the obtained solid when this invention persons freeze-dried the mixed aqueous solution of a polypeptide and a polyethylene glycol, by adding the organic solvent which may be melted and melting only a polyethylene glycol, a polyethylene glycol finds out that the polypeptide particle of a high grade is obtained as suspension, and came to complete this invention.
[0013] Since an organic solvent is not further contacted in the state of a solution according to this technique, without applying heat, physical impulse force, etc., denaturation and deactivation of a polypeptide hardly happen.
[0014] That is, although this invention freeze-dries a polypeptide and the mixed aqueous solution of a polyethylene glycol and a polypeptide must have been melted in the obtained solid, a polyethylene glycol is related with the atomization technique of the polypeptide characterized by adding the organic solvent which may be melted.
[0015]
[Embodiments of the Invention] In this invention, the mixed aqueous solution (the mixed aqueous solution is only called hereafter) which contains a polypeptide and a polyethylene glycol first is prepared.
[0016] As a polypeptide, it has a physiological activity useful for a mammalian, and the various peptides or various protein which can be used on clinical is mentioned. The thing of 1000-200000 is used for the molecular weight as a monomer, and, as for this polypeptide, the thing of 5000-70000 is especially used widely preferably. When it has a higher order structure in the field of biochemistry, the macromolecule classified into ******** protein is also contained in these polypeptides. Although the modality of polypeptide used by this invention is not limited especially as long as the purpose of this invention is attained, what has a certain fixed water solubility is desirable, and about 0.01mg /or more of the solubility is [ml] about 1mg/ml or more preferably at 20 degrees C to water.

[0017] As an example of a polypeptide, hormone, enzymes, and cytokines growth factors are mentioned, for example. The following polypeptides are more specifically mentioned.
[0018] As hormone, a growth hormone (GH), a growth hormone releasing (GRF), an insulin, a glucagon, a gastrin, a prolactin, an adrenocorticotrophin (ACTH), a thyrotropic hormone (TSH), a follicle stimulating hormone (FSH), a luteinizing hormone (LH), the human chorionic gonadotropin (hCG), a calcitonin, etc. are mentioned, for example.
[0019] enzymes ****** -- the [for example, an organization plasminogen ****** beta (tPA) a urokinase (UK), a streptokinase, protein C, ****** proteases, a superoxide De Dis mutase (SOD), and] -- VIII and IX factor, a peroxidase, etc. are mentioned
[0020] As cytokines, interferon (IFN-alpha, -beta, -gamma, etc.), interleukin (IL-1-IL-11 etc.), a cachectin, an oncostatin, colony stimulating factors (G-, M-, GM-CSF, etc.), a ********** ethyne (TPO), erythropoietin (EPO), etc. are mentioned, for example.
[0021] As growth factors, nerve growth factors (NGF-1, NGF-2, etc.), a neurotrophy factor (NTF), an epidermal growth factor (EGF), a platelet derived growth factor (PDGF), insulin Mr. growth factors (IGF-1, IGF-2, IGF-3, etc.), a fibroblast growth factor (aFGF, bFGF), osteogen growth factors (BMP-1, BMP-2, BMP-3, BMP-4, etc.), an atrial natriuresis factor (ANP), a cartilage inducer, etc. are mentioned,
[0022] Among these, as a desirable polypeptide, growth hormones (for example, 22 kilodalton human growth hormone, 20 kilodalton human growth hormone, etc.), interferon, erythropoietin, etc. are mentioned especially, for example.
[0023] These polypeptides may have the sugar chain and the sugar-chain structures may differ. Furthermore, these contain ********, a derivative, an analog, activity fragmentation, etc.
[0024] that from which the polypeptide used by this invention was obtained by the natural origin or

transgenics technique -- any are sufficient
[0025] moreover, as a polypeptide used by this invention May be a metal salt and as a metal in such a metal salt For example, alkaline earth metal (for example, calcium, magnesium, etc.), Zinc (II **), iron (II **, III **), copper (II **), tin (II **, IV **), aluminum (II **, III **), etc. are mentioned, and a polypeptide is called on these specifications also including what is these metals salt.
[0026] the polyethylene glycol used in this invention will be limited especially if usually used in the field of tablet technique -- not having -- such a polyethylene glycol ****** -- average molecular weight -- the thing of 400-500000 -- desirable -- the thing of 2000-100000 -- it divides and the thing of 6000-70000 is raised preferably
[0027] After the manufacture technique of the mixed aqueous solution may melt both polypeptide and polyethylene glycol in water at once and melts one side, it may melt another side, and it may mix the polypeptide aqueous solution and the polyethylene-glycol aqueous solution. Especially the method of preparation is not restricted just soluble [finally / the polypeptide and the polyethylene glycol] in water in short.
[0028] Although it will not be limited especially if it is within the limits which a polypeptide melts, if it dares illustrate the polypeptide concentration in the mixed aqueous solution, it is [ml] 1-100mg/ml preferably 0.1-200mg /.
[0029] Since a peptide will precipitate in the aqueous solution if it is made not much high too much although it will not be limited especially if it is within the limits which a polyethylene glycol melts, the concentration of the polyethylene glycol in the mixed aqueous solution is not desirable. If it dares illustrate the concentration of a desirable polyethylene glycol, 0.025-200mg /is [ml] 0.25-100mg/ml preferably.
[0030] Subsequently, although it freeze-dries and a polypeptide cannot melt the mixed aqueous solution in the obtained solid, a polyethylene glycol adds the organic solvent which may be melted and the target polypeptide particle is obtained as organic-solvent suspension by melting a polyethylene glycol.
[0031] Although the mixed aqueous solution is first frozen in freeze-drying the mixed aqueous solution, the conditions of a freeze which descend gradually are more desirable than the conditions on which the temperature of the mixed aqueous solution descends abruptly. Although it will be easily reached if such conditions are frozen using the freezer or freeze dryer whose setting temperature is -20--60 degree C and which is usually used, if such conditions are specified more concretely, an initial temperature fall speed (after cooling start descent temperature of the mixed aqueous solution per minute) is a part for about 10-30 degrees-C/preferably by about 2-40 degrees-C/.
[0032] The frozen mixed aqueous solution is decompressed and should just make moisture sublimate within a freeze dryer succeedingly according to a conventional method.
[0033] In this invention, in the freeze process of a freeze-drying process, in order to start the freezing from the water in the mixed aqueous solution to the beginning, in the fraction of a non-cryohydrate, concentration of a polypeptide and polyethylene-glycol concentration happens, and, as a result, the phase separation of the phase which was rich in the polypeptide, and the phase which was rich in the polyethylene glycol happens.
[0034] It is determined by the rate of the ratio of concentration of the polyethylene glycol/polypeptide in the mixed aqueous solution which phase-separation gestalt a polyethylene-glycol phase may form a minute drop into the case where the phase which was rich in the polypeptide forms a minute drop into the phase which was rich in the polyethylene glycol, and the phase which was rich in the polypeptide, and this phase-separation phenomenon becomes. If it is more than a certain constant value (phase inversion proportion is called) as which this rate of the ratio of concentration is determined with the modality of polypeptide, and the molecular weight of a polyethylene glycol, the phase which was rich in the polypeptide will form a minute drop into the phase which was rich in the polyethylene glycol. Generally, if the rate of the ratio of concentration is carried out more than phase inversion proportion, the globular form particle with a more small particle diameter will be obtained, if the rate of the ratio of concentration is made below into phase inversion proportion, a particle diameter will be a little large and the grain which carried out the indeterminate forms configuration will be obtained. Therefore, in order for the particle with a more

small particle diameter, for example, a mean particle diameter, to obtain a particle 10 micrometers or less, it is desirable to carry out the rate of the ratio of concentration more than phase inversion proportion.

[0035] Although phase inversion proportion is changed with the modality of polypeptide to use, and the molecular weight of a polyethylene glycol, suitably, it can prepare a particle using the mixed aqueous solution of the various rates of the ratio of concentration, and can determine it easily by investigating the particle diameter and its configuration. However, when a with a molecular weight of 6000 or more polyethylene glycol is used for phase inversion proportion, the difference in the molecular weight hardly influences, therefore phase inversion proportion is determined by only the modality of polypeptide to use. The phase inversion proportion in the case of it being thought that change of the phase inversion proportion by the modality of polypeptide originates in the molecular weight of a polypeptide greatly, therefore using a with a molecular weight of 6000 or more polyethylene glycol can be guessed to some extent with the molecular weight of the polypeptide to use. That is, as a polyethylene glycol, when a with a molecular weight of 6000 or more thing is used, in approximation, between the molecular weight (M) of a polypeptide, and phase inversion proportion (T), the following relational expression T= 102.7/M0.68 is realized, and it can ask for phase inversion proportion in the above-mentioned formula by substituting the molecular weight of the polypeptide to use.

[0036] Although changed like the above according to the modality of polypeptide which uses phase inversion proportion etc., if a mean particle diameter dares illustrate a rate of the ratio of concentration from which a particle 10 micrometers or less is obtained, it is one or more more preferably 0.5 or more 0.25 or more.

[0037] What is necessary is not to be restricted but just to choose a polyethylene glycol suitably especially, as an organic solvent used for this invention, according to the modality of used polypeptide, if, so that the solubility of what may be melted, for example, the polypeptide in 20 degrees C, may be 1mg/ml or less and the solubility of a polyethylene glycol may be 1mg/ml or more, although a polypeptide must have been melted. If it dares illustrate the example of such an organic solvent, for example A methylene chloride, Halogenated hydrocarbons, such as chloroform and a carbon tetrachloride, methyl acetate, Lower alcohols, such as acetic ester, such as ethyl acetate and butyl acetate, a methanol, and ethanol Aromatic hydrocarbons, such as benzene, toluene, a xylene, and a cumene, ethyl ether, The others which are ketones, such as ether, such as a tetrahydrofuran, and an acetone A pentane, an acetonitrile, a pyridine, etc. are raised, among these a methylene chloride, chloroform, an acetone, an acetonitrile, ethyl acetate, toluene, a methanol, and especially ethanol are desirable, two or more sorts may be mixed and these organic solvents may be used.

[0038] Moreover, the solubility to water is low for volatilities, such as a methylene chloride, chloroform, toluene, and ethyl acetate, among the above-mentioned organic solvents, and if what a biodegradation nature polymer melts is used, when using for a microsphere tablet the polypeptide particle obtained by this technique, it is also possible to perform a particle manufacture process and a microsphere manufacture process continuously.

[0039] In this invention, since the polypeptide is already in the status that it distributed in the polyethylene glycol as a particle, in the phase of the solid obtained by freeze drying, a polypeptide particle is obtained only by melting a polyethylene glycol using an organic solvent, and detailed-ized means, such as trituration and a ultrasonic irradiation, are not needed.

[0040] If the obtained polypeptide particle suspension is required, the polyethylene glycol which is melting into solvent exchange or particle suspension using known means, such as dialysis, centrifugal separation and washing, and filtration, washing, is also removable. Moreover, a solvent is removed using means, such as **** or centrifugal separation, and it is also possible to take out a particle as fine particles by making it dry.

[0041] By the known means, the obtained polypeptide particle can be made a spraying tablet, a microsphere tablet, etc.

[0042] A spraying tablet is polypeptide particle independent [which was taken out from suspension as fine particles], or adds a surfactant for the enhancement in dispersibility of a particle, and is prepared. As a surfactant, sorbitan trioleate, a soybean lecithin, oleyl alcohol, a hydrogenated-castor-

oil derivative, etc. are raised, and the loadings are 0.001 - 5% (w/w) of a domain to a polypeptide weight, and are 0.05 - 2% (w/w) preferably, for example.
[0043] Moreover, the stabilizing agent, the excipient, etc. may be added if needed. As a stabilizing agent, a man serum albumin, gelatin, etc. are raised and 0.01 - 200% of the polypeptide weight (w/w) of the loadings is desirable. As an excipient, sugar or sugar-alcohol, such as a lactose, a maltose, sorbitose, a trehalose, a xylose, a mannitol, a sorbitol, and xylitose, is raised, and the loadings are 0.01 - 200% (w/w) of within the limits to a polypeptide weight, and are 1 - 50% (w/w) preferably.
[0044] Furthermore, in order to blend suitably mineral ion required for the osmotic-pressure maintenance which originally exists in a living body, for example, a calcium ion, magnesium ion, sodium ion, potassium ion, ****** ion, etc. and to suppress stimulative [to a living body], the surfactant of the alveoli-pulmonis origin may also be blended if needed.
[0045] thus, the prepared polypeptide constituent for a spraying tablet -- as it is -- or the compressed air, compression carbon dioxide gas, etc. -- spraying gas -- carrying out -- moreover -- or it distributes in a suitable propellant and is made to inhale in the pharynx section or lungs via the inside of an oral cavity or a nasal cavity As an usable propellant, chlorofluorocarbon (chlorofluocarbon 11 and 12,114 etc.), the ****** fluorocarbons (chlorofluocarbon 123, 124, and 141b etc.) containing hydrogen, the fluorocarbons (chlorofluocarbon 125 and 134a etc.) that do not contain chlorine are raised.
[0046] What is necessary is to prepare the "oil phase" by which the polypeptide particle was distributed in the organic solvent with the low solubility to water for the volatility which the biodegradation nature polymer is melting, and just to prepare by solidifying the biodegradation nature polymer in this oil phase, when considering as a microsphere tablet. When two or more sorts of biodegradation nature polymers exist in an oil phase, they may carry out a phase separation mutually and may form O / O type emulsion.
[0047] Although a polypeptide must have been melted in the solid which an oil phase adds the organic solvent with low solubility and biodegradation nature polymer to water for the volatility which cannot melt a polypeptide in polypeptide particle powder and may melt a biodegradation nature polymer in it, or was obtained by freeze-drying a polypeptide and the mixed aqueous solution of a polyethylene glycol, for the volatility which may be melted, the solubility to water adds a low organic solvent, and can prepare a polyethylene glycol and a biodegradation nature polymer. Since the operation which takes out a polypeptide particle as powder is unnecessary when the polypeptide microsphere of a high content is obtained and an oil phase is prepared by the latter technique in order that a polyethylene glycol may not mix into a microsphere, when an oil phase is prepared by the former technique, it is advantageous on the manufacture.
[0048] As an example of the organic solvent with the low solubility to water, a methylene chloride, chloroform, ethyl acetate, toluene, etc. are raised with the volatility which cannot melt and may melt a biodegradation nature polymer, among these a methylene chloride and especially chloroform of a polypeptide are desirable, and these organic solvents may mix and use two or more sorts.
[0049] Although a polypeptide must have been melted, as an example of the organic solvent with the low solubility to water, the above-mentioned methylene chloride, chloroform, ethyl acetate, toluene, etc. are raised with the volatility which may be melted, among these a polyethylene glycol and a biodegradation nature polymer have a methylene chloride and especially desirable chloroform, and these organic solvents may mix and use two or more sorts.
[0050] If it is the polymer which has the property which does not have a physiological activity, but decomposes and disappears as a biodegradation nature polymer in the living body, it is good anything. For example, homopolymers, such as a lactic acid, a glycolic acid, a malic acid, and hydroxybutyric acid, and these copolymers are raised. The polylactic acid and lactic-acid glycolic-acid copolymer of 1000-500000 have especially desirable average molecular weight.
[0051] Although the content of a polypeptide to a biodegradation nature polymer can be chosen arbitrarily and changes with the modality of polypeptide, the pharmacology effect made into the purpose, and exudation time, it is [about 0.01 - 40% (w/w) of abbreviation] especially desirable. [0.01 - 20% of]
[0052] Although the concentration of the biodegradation nature polymer in an oil phase changes with the molecular weight of a biodegradation nature polymer, modalities of organic solvent, etc., that

what is necessary is just to usually consider as about 0.01% (w/w) - about 80% (w/w) of a domain, it is divided preferably about 0.1% (w/w) to about 70% (w/w), and is about 1% (w/w) - about 60% (w/w) preferably.

[0053] As means to solidify the biodegradation nature polymer in an oil phase, the liquid drying of the various emulsions of O/O / O/W type, and W type, a phase-separation method, a spray-drying method, etc. are raised, and such technique is explained below.

[0054] (a) What is necessary is to prepare O / W type emulsion and just to dry the obtained emulsion among liquid by adding the oil phase prepared by the above-mentioned technique into the aqueous phase, and emulsifying it, in order to prepare a microsphere by O / the W type emulsion liquid-drying:book technique.

[0055] That what is necessary is just to carry out for example, by about 10000 times [about 1 time to] the oil phase volume, an aqueous-phase volume is divided and it is it preferably twice [about] to about 5000 times. [of this] [about 2000 times / about 5 times to]

[0056] In order to prevent a coalescence of an oil phase, and the generated flocculation of a microsphere, a flocculation inhibitor can also be added to the aqueous phase. As a flocculation inhibitor, if generally used, although it is good, polyvinyl alcohol, a polyvinyl pyrrolidone, a methyl cellulose, gum arabic, chitosan, gelatin, a serum albumin, a surfactant, etc. will be raised anything, for example. 0.1 - 2% (w/v) of especially the concentration in the aqueous phase of a flocculation inhibitor is desirable 0.01 to 10% (w/v). By changing the modality and addition concentration of emulsion stabilizer, the particle diameter of a microsphere and a distribution of grain size are controllable.

[0057] Furthermore in the aqueous phase, it is. PH regulators (for example, an acetic acid, a hydrochloric acid, a sodium hydroxide, etc.), preservatives, such as for example, para oxy-benzoic acids, and osmotic-pressure regulators (for example, saccharides, such as salts, such as a sodium chloride, and a mannitol etc.) may be added.

[0058] Emulsification operation can be easily carried out with a propeller formula agitator, a turbine type emulsifier, ultrasonic variance equipment, or a hyperbaric-pressure emulsifier.

[0059] The temperature up of the xeransis among liquid is carried out, being able to carry out by conventional methods, such as the heating method and a reduced pressure method, for example, agitating an emulsion with a propeller type or a turbine type agitator by the heating method, and it distills off a solvent. although this agitating speed is changed a little by equipment and the charge -- about 10- it is 50 - 10000rpm especially preferably about 25000 rpm What is necessary is just to raise temperature over abbreviation 0.5- about 4 hours. The maximum temperature after 0-25 degrees C and elevation has [the first temperature] desirable 25-50 degrees C. Moreover, in a reduced pressure method, an emulsion is gradually decompressed with a suitable decompression device like a rotating evaporator, it is referred to as about 0.1-50mm / Hg, and a solvent is distilled off.

[0060] The particle diameter of the microsphere obtained is 0.01 micrometers - 500 micrometers as a mean particle diameter, and, generally the particle diameter of the microsphere obtained becomes detailed by raising the proportion to the amount of polymers of the amount of organic solvents in an oil phase.

[0061] Thus, after isolating preparatively by centrifugal separation or filtration operation, again, the obtained microsphere carries out the repeat washing elimination of the emulsion stabilizer adhering to a microsphere front face etc. several times with distilled water, it distributes to distilled water etc., and if required, additives, such as a mannitol, will be added and it will freeze-dry it. Then, as long as it is required, it may warm under reduced pressure and the moisture and organic solvent in a microsphere may be removed. warming -- what is necessary is just to hold at about 1 hour or 24 hours, and this temperature more preferably the 2 or 3rd [less than] day less than one week, after warming to temperature higher about 5 degrees C or more than the midpoint glass transition temperature of the in-the-living-body fitting polymer which asked for the microsphere by the differential scanning calorimeter as conditions, for example by the per minute 10-20-degree C programming rate and reaching temperature predetermined in the microsphere itself

[0062] (b) In order to prepare a microsphere by O/O / the W type emulsion liquid-drying:book technique, prepare an oil phase using two or more sorts of biodegradation nature polymers (although

it is melting into an organic solvent, respectively, two kinds of polymers here). It does not dissolve mutually, but each phase emulsifies this which is carrying out the phase separation, makes it O / O type emulsion, prepares O/O / W type emulsion by adding this O / O type emulsion into the aqueous phase like (a), and emulsifying it, and should just dry the obtained emulsion among liquid.
[0063] When the combination of two kinds of polymers used here mixes each organic solution, it does not dissolve, but if each phase is combination in which one polymer (the first polymer) forms an alloy in the polymer (the second polymer) of another side, anything, it is good, for example, has the combination of a polylactic acid and a lactic-acid glycolic-acid copolymer. Moreover, each can use these firsts and the second polymer also in the type of the mixture of two or more sorts of polymers.
[0064] Since the polymer with many operating weights forms a continuity layer in O / O type emulsion, and generally turns into the second polymer, and the polymer with few operating weights distributes in this continuity layer of O / O type emulsion, forms a minute drop and turns into the first polymer, the first polymer and the second polymer can choose it, being able to use this as an index. That what is necessary is just to determine the weight ratio of the first polymer and the second polymer to use based on the above-mentioned index, although there is especially no limit, that whose second polymer the first polymer is 1-10 to 1, for example is raised. Among these, as a desirable weight ratio, the thing of 2-4 is raised [the first polymer] for the second polymer to 1. For example, in the case of the combination of a polylactic acid and a lactic-acid glycolic-acid copolymer, both molecular weight is the same, and when a polylactic acid is [2 and a lactic-acid glycolic-acid copolymer] 1 for a weight ratio, a lactic-acid glycolic-acid copolymer forms a minute drop, and turns into the first polymer. Moreover, in the case of the above-mentioned combination, when a weight ratio is reverse, a polylactic acid forms a minute drop and becomes the first polymer. Moreover, a polypeptide particle is unevenly distributed in one of polymer solutions with the difference in compatibility to the first or the second polymer. Therefore, in this technique, the microsphere which was made to contain a polypeptide in the polymer which forms a minute drop, and was excellent in sustained-release can be obtained using the above-mentioned relation. For example, since it becomes possible to make a polypeptide particle contain in a minute drop by changing the weight ratio of a polymer when a polypeptide particle is unevenly distributed in a continuous phase (namely, the second polymer) in O / O type emulsion, the combination of a polypeptide and a polymer can be chosen easily. Moreover, if viscosity generally rises, since the coalescence between grain will be suppressed, O / O type emulsion is stable. When the particle diameter of an internal minute field can ** a parvus microsphere and adopts the thing of the amount of macromolecules as one polymer among two sorts of biodegradation nature polymers Like the above, the particle diameter of an internal minute field may be able to manufacture a parvus microsphere, and can control the particle diameter of a minute field in the interior of a microsphere.
[0065] Therefore, the microsphere tablet obtained by this technique is a polynuclear microsphere tablet whose minute field which consists of two or more sorts of biodegradation nature polymers, and consists of one biodegradation nature polymer (the first polymer) has the internal structure currently distributed all over the field which consists of a biodegradation nature polymer (the second polymer) of another side, and contains a polypeptide all over this minute field.
[0066] In this technique, the effect of the first polymer and the second polymer is as follows, respectively. To a polypeptide, since the first polymer has compatibility higher than the second polymer, it can hold a polypeptide alternatively. The second polymer has two effects greatly. In case O / O type emulsion prepared by this technique are further emulsified in the aqueous phase and it considers as O/O / W type emulsion in the first place, it has the effect which does not miss the polypeptide held to the first polymer in the aqueous phase. The high rate of incorporation is obtained by this. When a microsphere touches [second] body fluid, as a result of the alloy of the internal phase who consists of the first polymer holding the polypeptide preventing contacting direct water, it has the effect of exudation controls, such as suppression of early bursty elution.
[0067] What is necessary is for the obtained microsphere to wash like (a) and just to freeze-dry it subsequently.
[0068] (c) What is necessary is to add a coacervation agent to an oil phase gradually under churning. and just to carry out precipitation solidification of the microsphere, in manufacturing a microcapsule

by the phase-separation method (coacervation method):book method.
[0069] A volume about 2,000 times [about 0.01 times to] the amount of volumes of an oil phase is applied, and it is about 0.05 times to about 500 times preferably, and a coacervation agent is divided and is about 200 times [about 0.1 times to] the amount of volumes of this preferably. Moreover, a coacervation agent is a macromolecule, straight mineral oil, or vegetable oil etc. which carries out a mixing to the **** organic solvent for oil phases, and especially if it is the compound which does not melt a biodegradation nature polymer, it will not be limited. Specifically, silicone oil, the sesame oil, soybean oil, a cone oil, cotton seed oil, a coconut oil, the linseed oil, straight mineral oil, n-hexane, n-heptane, etc. are used. Two or more sorts may be mixed and these may be used.
[0070] What is necessary is to wash the obtained microsphere by the heptane etc. repeatedly, to remove a coacervation agent, to wash still like (a), and just to freeze-dry it subsequently, after isolating preparatively by centrifugal separation or filtration operation.
[0071] (d) In manufacturing a microsphere by the spray-drying method:book method, an oil phase is sprayed into the drying room of a spray dryer (spray dryer) using a nozzle, and it volatilizes the organic solvent in a spraying drop extremely for a short time.
[0072] As a nozzle, there are a two-fluid-nozzle type, a pressure-nozzle type, a rotation disk type, etc., for example.
[0073] If the obtained microsphere is required, it is warmed under reduced pressure like the above (a), and should just remove the moisture and organic solvent in a microsphere.
[0074] (a) It is the most desirable to prepare among the technique of - (d) by the liquid drying from O/O / W type emulsion from fields, such as a rate of incorporation of a polypeptide, the suppression luminous efficacy of an initial-burst phenomenon, and recovery.
[0075] A living body can be medicated with the obtained microsphere as a **** agent as it is. Moreover, it can use also as a raw material at the time of manufacturing various tablets. As such a tablet, the injection, an internal use agent, an endermic medication agent, a suppository, a pernasal medication agent, an oral-cavity medication agent, the medication agent in an eye, etc. are raised, for example.
[0076] Hereafter, a case of the operation explains this invention in detail further.
[0077]
[Example] The aqueous solution of 5% of case-of-the-operation 1 bovine serum albumins (molecular weight 67000, product made from a sigma) (w/v), the polyethylene-glycol 6000(product made from Wako pure medicine) 5% (w/v) aqueous solution, and the purified water were mixed suitably, and it prepared 1ml (rates 0-3 of the ratio of concentration) of the aqueous solutions with a bovine-serum-albumin concentration [of 10mg/ml], and a polyethylene-glycol concentration of 0-30mg [/ml] at a time, respectively. After freezing these aqueous solutions at -45 degrees C, it freeze-dried using the freeze dryer (product made from a KYOWA VAC RLE-52ES:republican vacuum technology) (degree of vacuum about 0.02 torrs, -20 degree-C 3 hours, and 20 degree-C about 12 hours), and 2ml of methylene chlorides was added to the obtained solid, and bovine-serum-albumin particle suspension was obtained.
[0078] The result which measured the mean particle diameter of the particle obtained using the laser diffraction formula particle-size-distribution measuring device (SALD-1100:Shimadzu make) was shown in drawing 1 .
[0079] In 0.25 or more rates of the ratio of concentration, the particle 10 micrometers or less was obtained for the mean particle diameter.
[0080] It was the grain of the indeterminate forms configuration as for which the circular hole was vacant in the case of the rate 0.1 of the ratio of concentration as it was shown in drawing 3 to being the particle of a globular form [case / of the rate 0.5 of the ratio of concentration] as shown in drawing 2 , when the particle which was obtained in the case of the rates 0.5 and 0.1 of the ratio of concentration was observed under the microscope. It is thought that the circular hole observed by the grain obtained at the rate 0.1 of the ratio of concentration is the trace of the polyethylene-glycol phase which turned into the dispersed phase at the time of a phase separation.
[0081] in drawing 1 , a clear folding point exists in the rates 0.2-0.25 of the ratio of concentration, and if the rate of the ratio of concentration is beyond the value of this folding point, since the particle diameter of the grain obtained is markedly alike to the particle of 10 micrometers or less of mean

particle diameters being obtained in below the value of this folding point and it is large, it is presumed that phase inversion proportion is this folding point, 0.2-0.25, [i.e.,]
[0082] case-of-the-operation 2 case of the operation 1 -- setting -- a polyethylene glycol 6000 -- changing -- a polyethylene glycol 2000 -- said -- 4000 -- said -- 20000 (all are the products made from the Katayama chemistry) -- and -- said -- using 70000 (product made from Wako pure medicine), the same experiment was conducted, it asked for the phase inversion proportion at the time of using the polyethylene glycol of each molecular weight like the case of the operation 1, and the relation between polyethylene-glycol molecular weight and phase inversion proportion was shown in drawing 4
[0083] The phase inversion proportion at the time of using polyethylene glycols 20000 and 70000 is almost of the same grade as the phase inversion proportion at the time of using a polyethylene glycol 6000, and when a with a molecular weight of 6000 or more polyethylene glycol is used, change of the phase inversion proportion by the difference in the molecular weight is considered to be a few thing.
[0084] Moreover, when the polyethylene glycol of which molecular weight was used, particle about 10 micrometers or less was obtained by carrying out the rate of the ratio of concentration to more than phase inversion proportion.
[0085] In case-of-the-operation 3 case of the operation 1, it changes to a bovine serum albumin. Gelatin D (molecular weight 3000, product made from ******), Gelatin A (molecular weight 7000, product made from ******), a Bowman Birk inhibitor (molecular weight 8000, product made from a sigma), A soybeans trypsin inhibitor (molecular weight 20100, product made from a sigma), a superoxide dismutase (molecular weight 32000, product made from a sigma), The same experiment was conducted using horseradish peroxidase (molecular weight 40000, product made from Wako pure medicine), it asked for the phase inversion proportion at the time of using each polypeptide like the case of the operation 1, and the relation between polypeptide molecular weight and phase inversion proportion was shown in drawing 5 .
[0086] The straight-line relation was realized in the logarithm of polypeptide molecular weight, and the logarithm of phase inversion proportion, the relation of formula LogT=-0.68LogM+2.7 was realized in approximation between the molecular weight (M) of a polypeptide, and phase inversion proportion (T), therefore it turns out that phase inversion proportion (T) is expressed as T= 102.7/M0.68 with polypeptide molecular weight (M) so that clearly from drawing 5 .
[0087] Moreover, when which polypeptide was used, particle about 10 micrometers or less was obtained by carrying out the rate of the ratio of concentration to more than phase inversion proportion.
[0088] 250mg (product made from a sigma) of case-of-the-operation 4 bovine serum albumins and polyethylene-glycol 6000 (product made from Wako pure medicine) 250mg were melted in 10ml of purified waters, and the mixed aqueous solution was prepared. After freezing this aqueous solution at -45 degrees C, it freeze-dried using the freeze dryer (product made from a KYOWA VAC RLE-52ES:republican vacuum technology) (degree of vacuum about 0.02 torrs, -20 degree-C 3 hours, and 20 degree-C about 12 hours), and 10ml of methylene chlorides was added to the obtained solid, and bovine-serum-albumin particle suspension was obtained. The bovine-serum-albumin particle was ****ed from this suspension using the membrane filter (Millipore make) of 0.22 micrometers of apertures, and it washed this at a time twice by 10ml of methylene chlorides further. It was made to dry under reduced pressure of the obtained particle overnight, and the bovine-serum-albumin particle was obtained as powder.
[0089] It was 4.77 micrometers when the mean particle diameter of a bovine-serum-albumin particle was measured using the laser diffraction formula particle-size-distribution measuring device (SALD-1100:Shimadzu make).
[0090] Moreover, when the amount of proteins of the obtained particle was measured and the bovine-serum-albumin content in a particle was investigated, it was 99.2% and was very a high content.
[0091] 0.1ml of the aqueous solutions and 0.9ml of purified waters were mixed 5mg [of case-of-the-operation 5 horseradish peroxidase] (product made from Wako pure medicine), and polyethylene-glycol 6000(product made from Wako pure medicine) 5% (w/v), and the mixed aqueous solution

was prepared. After freezing this aqueous solution at -45 degrees C, it freeze-dried using the freeze dryer (product made from a KYOWA VAC RLE-52ES:republican vacuum technology) (degree of vacuum about 0.02 torrs, -20 degree-C 3 hours, and 20 degree-C about 12 hours). 2ml of methylene chlorides was added to the obtained solid, and horseradish peroxidase particle suspension was obtained.

[0092] It was 4.08 micrometers when the mean particle diameter of a particle was measured using the laser diffraction formula particle-size-distribution measuring device (SALD-1100:Shimadzu make).

[0093] Moreover, the solvent (methylene chloride) was distilled out of the obtained particle suspension, and when the residue was melted in the purified water and the peroxidase activity was measured, deactivation of the enzyme activity in this atomization process did not accept.

[0094] 25mg (product made from a sigma) of case-of-the-operation 6 bovine serum albumins, polyethylene-glycol 6000 (product made from Wako pure medicine) 15mg, and 1ml of purified waters were mixed, and the mixed aqueous solution was prepared. a freeze dryer (product made from a KYOWA VAC RLE-52ES:republican vacuum technology) after freezing this aqueous solution at -45 degrees C -- using -- freeze drying (a degree of vacuum -- about 0.02 torrs) - the solid which carries out for about 12 hours and was obtained 20 degrees C 20 degrees C for 3 hours -- PLGA5020 (a lactic-acid glycolic-acid copolymer --) the mole ratio of molecular weight 20000, a lactic acid, and a glycolic acid -- 50:50 and the product made from Wako pure medicine -- 184mg PLA0020 (polylactic-acid, molecular weight 20000, product made from Wako pure medicine) 248.4mg, 1.85g of methylene chlorides is added. The polyethylene glycol in a solid, After having melted PLGA5020 and PLA0020 and distributing a polypeptide particle, added PLA00110 (l body polylactic-acid, molecular weight 110000, product made from ********** in **********) 27.6mg, it was made to melt, and O / O type emulsion was prepared. This O / O type emulsion are added in 4ml of 15-degree C 0.25% (w/w) methyl-cellulose aqueous solutions. It emulsifies using a poly-TRON homogenizer (8000rpm, 5 minutes, product made from kinematica). Preparing O/O / W type emulsion, moving this into a purified water (15 degrees C and 400ml), and stirring by 400rpm with the paddle with four sheet feather (a three one motor, product made from new east science), the temperature up was carried out to 15-30 degrees C over 3 hours, xeransis among liquid was performed, and the microsphere was made to form. After carrying out the sieving of the distributed liquid of the obtained microsphere in a 150-micrometer mesh, in a 20-micrometer mesh, the microsphere was ****ed and it freeze-dried.

[0095] Obtained microsphere 50mg was put into the test tube with a plug, 10ml (0.02% (w/v) sodium-azide inclusion PBS) of eluates was added, and the incubation was carried out with the rotation-culture vessel (25rpm, 37 degrees C). The eluate was newly added and the incubation was continued, after having taken out the test tube from the incubator, having carried out centrifugal separation (2000rpm, 5 minutes) with time and removing 9ml of supernatant liquids. The amount of proteins of the extracted supernatant liquid was measured, and the amount of bovine serum albumins emitted from the microsphere after fixed time progress was calculated. A result is shown in drawing 6 .

[0096] The obtained microsphere emitted the bovine serum albumin at the fixed speed over about 21 days, and the rate of an initial burst was also very low so that clearly from drawing 6 .

[0097] 500mg (product made from a sigma) of case-of-the-operation 7 bovine serum albumins and polyethylene-glycol 6000 (product made from Wako pure medicine) 500mg were melted in 20ml of purified waters, and the mixed aqueous solution was prepared. After freezing this aqueous solution at -45 degrees C, it freeze-dried using the freeze dryer (product made from a KYOWA VAC RLE-52ES:republican vacuum technology) (degree of vacuum about 0.02 torrs, -20 degree-C 3 hours, and 20 degree-C about 12 hours), and 20ml of methylene chlorides was added to the obtained solid, and bovine-serum-albumin particle suspension was obtained. The bovine-serum-albumin particle was ****ed from this suspension using the membrane filter (Millipore make) of 0.22 micrometers of apertures, and it washed this at a time twice by 20ml of methylene chlorides further. It was made to dry under reduced pressure of the obtained particle overnight, and the bovine-serum-albumin particle was obtained as powder.

[0098] Beforehand PLGA5020 (mole ratio of lactic-acid glycolic-acid copolymer, molecular weight

20000, lactic-acid, and glycolic acid is 50:50 and product made from Wako pure medicine) 190mg, PLA0020 (polylactic-acid, molecular weight 20000, product made from Wako pure medicine) 256.5mg is melted in 1.85g of methylene chlorides. After making this distribute the 25mg of the above-mentioned bovine-serum-albumin particle powder, PLA00110 (l body polylactic-acid, molecular weight 110000, product made from ********** in **********) 28.5mg was added, this was melted, and O / O type emulsion was prepared. This O / O type emulsion are added in 4ml of 15-degree C 0.25% (w/w) methyl-cellulose aqueous solutions. emulsifying using a poly-TRON homogenizer (8000rpm, 5 minutes), preparing O/O / W type emulsion, moving this into a purified water (15 degrees C and 400ml), and stirring by 400rpm with the paddle with four sheet feather The temperature up was carried out to 15-30 degrees C over 3 hours, xeransis among liquid was performed, and the microsphere was made to form. After carrying out the sieving of the distributed liquid of the obtained microsphere in a 150-micrometer mesh, in a 20-micrometer mesh, the microsphere was ****ed and it freeze-dried.

[0099] Obtained microsphere 50mg was put into the test tube with a plug, 10ml (0.02% (w/v) sodium-azide inclusion PBS) of eluates was added, and the incubation was carried out with the rotation-culture vessel (25rpm, 37 degrees C). The eluate was newly added and the incubation was continued, after having taken out the test tube from the incubator, having carried out centrifugal separation (2000rpm, 5 minutes) with time and removing 9ml of supernatant liquids. The amount of proteins of the extracted supernatant liquid was measured, and the amount of bovine serum albumins emitted from the microsphere after fixed time progress was calculated. A result is shown in drawing 7 .

[0100] The obtained microsphere emitted the bovine serum albumin at the fixed speed over about 21 days, and the rate of an initial burst was also very low so that clearly from drawing 7 .

[0101]

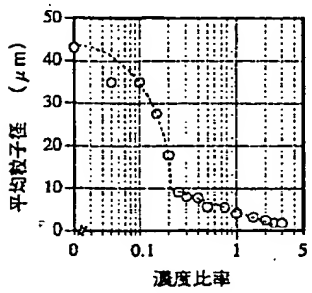
[Effect of the Invention] Since according to this invention it is accompanied neither by heat nor physical collision and an organic solvent is not contacted in the state of the aqueous solution, the polypeptide particle which can carry out the atomization of the polypeptide, without being accompanied by denaturation, and was obtained is very a high grade, and redispersible is good.

[0102] Moreover, according to this invention, since a loss hardly arises at the time of particle recovery, recovery is about 100%.

[0103] Furthermore, if the polypeptide particle obtained by this invention is used, a polypeptide can be emitted at a fixed speed over a long period of time, and the very low high content microsphere tablet of the rate of an initial burst will be obtained easily.

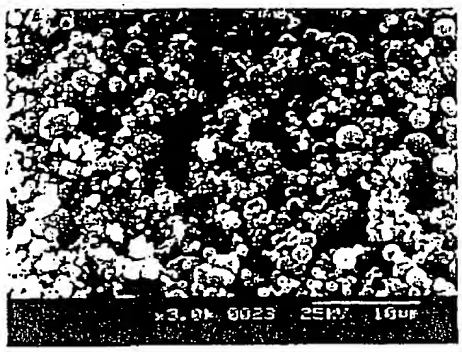
[Translation done.]

Drawing selection Drawing 1



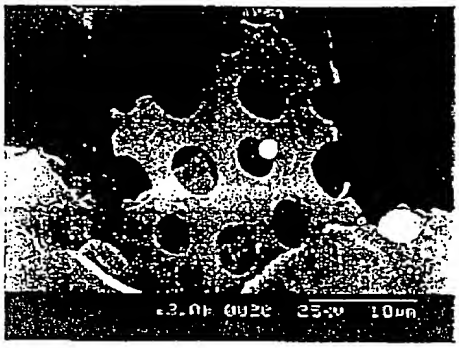
[Translation done.]

Drawing selection Drawing 2



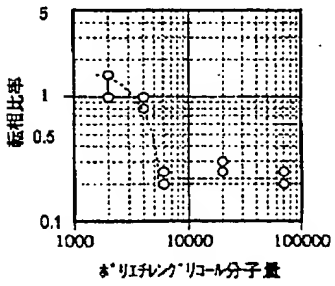
[Translation done.]

Drawing selection Drawing 3



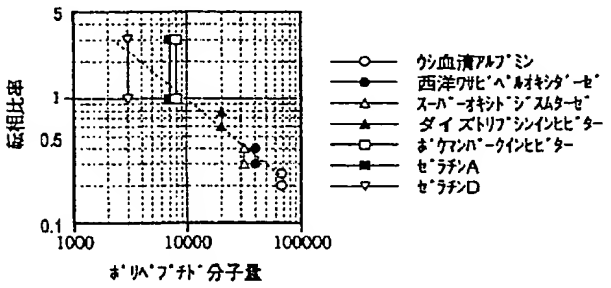
[Translation done.]

Drawing selection Drawing 4



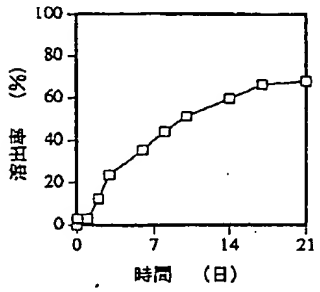
[Translation done.]

Drawing selection Drawing 5



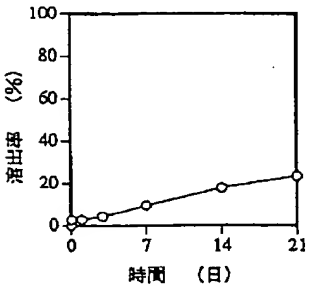
[Translation done.]

Drawing selection Drawing 6



[Translation done.]

Drawing selection Drawing 7



[Translation done.]